

EXHIBIT 67

UPDATE: Mycobacterium chimaera Infections Associated with LivaNova PLC (formerly Sorin Group Deutschland GmbH) Stöckert 3T Heater-Cooler System: FDA Safety Communication

The FDA is updating its June 1, 2016 [Safety Communication \(/MedicalDevices/Safety/AlertsandNotices/ucm504213.htm\)](#) to provide new information about *Mycobacterium chimaera* (*M. chimaera*) infections associated with the use of the 3T in U.S. patients who have undergone cardiothoracic surgeries. This communication also contains updated recommendations to help prevent the spread of infection related to the use of these devices.

October 13, 2016

Audiences:

- Health care providers who use 3T Heater-Cooler System
- Primary care providers who are responsible for the ongoing care of patients who have undergone cardiothoracic surgery
- Patients who have undergone cardiothoracic surgery
- Hospital staff who are responsible for operating and maintaining 3T Heater-Cooler System
- Health care facilities that perform procedures using the 3T Heater-Cooler System

Medical Specialties: Cardiothoracic Surgeons, Cardiovascular Surgeons, Orthopedic Surgeons, Neurosurgeons, General Surgeons, Anesthesiologists, Infection Control, Infectious Disease Physicians, Pediatrics, Primary Care, and Intensive Care Physicians

Product: The Stöckert 3T Heater-Cooler System (3T), manufactured by LivaNova PLC (formerly Sorin Group Deutschland GmbH), is intended to provide temperature-controlled water to 1) oxygenator heat exchangers, 2) cardioplegia (paralysis of the heart) heat exchangers, and/or 3) warming/cooling blankets to warm or cool a patient during cardiopulmonary bypass procedures lasting six hours or less.

Purpose: The FDA is updating its June 1, 2016 [Safety Communication \(/MedicalDevices/Safety/AlertsandNotices/ucm504213.htm\)](#) to provide new information about *Mycobacterium chimaera* (*M. chimaera*) infections associated with the use of the 3T in U.S. patients who have undergone cardiothoracic surgeries. This communication also contains updated recommendations to help prevent the spread of infection related to the use of these devices.

As the FDA continues to investigate infections associated with the 3T, we believe health care facilities should take additional steps to help mitigate the risk of infection associated with the use of these devices

Summary of Problem and Scope:

Heater-cooler devices

(<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/CardiovascularDevices/Heater-CoolerDevices/>) are commonly used during cardiothoracic surgeries, as well as other medical and surgical procedures, to warm or cool a patient in order to optimize medical care and improve patient outcomes. Heater-cooler devices have water tanks that provide temperature-controlled water to external heat exchangers or warming/cooling blankets through closed circuits. Although the water in the circuits does not come into direct contact with the patient, there is the potential for contaminated water to enter other parts of the device and aerosolize, transmitting bacteria through the air and through the device's exhaust vent into the environment and to the patient. In October 2015, the FDA issued a **Safety Communication** ([/MedicalDevices/Safety/AlertsandNotices/ucm466963.htm](http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm466963.htm)) to provide recommendations to help minimize patient risk of infections associated with heater-cooler devices. Since issuing that communication, the FDA has continued to evaluate the causes and risk factors for transmission of microbial agents associated with heater-cooler devices and has collaborated with professional societies, public health partners, and experts to develop strategies to minimize patient exposure.

A European study¹ published in April 2016 describes a link between *M. chimaera* clinical samples from several European infected cardiothoracic patients, samples from the heater-cooler devices used during these patient's procedures, and environmental samples from the device manufacturer's production and servicing facility in Germany. The results of this paper suggest a direct link between the *M. chimaera* that infected European patients during open-chest cardiac surgery, and the *M. chimaera* isolated from the 3T heater-cooler model utilized during these patients' surgeries.

M. chimaera is a type of nontuberculous mycobacterium (NTM) classified as a slow grower. *M. chimaera* may cause serious illness or death. The FDA believes *M. chimaera* infections associated with the 3T are rare. However, they are difficult to detect because infected patients may not develop symptoms or signs of infection for months to years after initial exposure.

On June 1, 2016, the FDA issued a **Safety Communication** ([/MedicalDevices/Safety/AlertsandNotices/ucm504213.htm](http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm504213.htm)) specific to *M. chimaera* infections associated with the use of the 3T. Testing conducted by the manufacturer in August 2014 found *M. chimaera* contamination on the production line and water supply at the 3T manufacturing facility. The 3T devices manufactured at this facility were distributed worldwide. In response to the *M. chimaera* findings in August 2014, the manufacturer added cleaning and disinfection procedures to the production line in September 2014. Samples taken at the same manufacturing facility, by the German Regulatory Authorities in July 2015 did not show *M. chimaera*, potentially indicating the contamination at the manufacturing facility had been resolved. Although the manufacturer of 3T devices added cleaning and disinfection procedures to the production line in September 2014, the FDA is now aware of some 3T devices manufactured after September 2014 which have tested positive for *M. chimaera*. It has not been confirmed whether these devices were contaminated at the manufacturing facility or became contaminated at the user facility. To date, the FDA is not aware of *M. chimaera* patient infections associated with 3T devices that were manufactured after September 2014.

The June 1, 2016 **Safety Communication** ([/MedicalDevices/Safety/AlertsandNotices/ucm504213.htm](http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm504213.htm)) also stated the FDA received reports of U.S. patients infected with *M. chimaera* after undergoing cardiothoracic surgery that involved use of the 3T devices. Each of those reports related to 3T devices that were manufactured prior to September 2014. The Centers for Disease Control and Prevention (CDC) in conjunction with National Jewish Health has **performed** (https://www.cdc.gov/mmwr/volumes/65/wr/mm6540a6.htm?s_cid=mm6540a6_w) whole genome sequencing on clinical isolates from infected patients and samples taken from the 3T devices from hospitals

representing geographically distinct regions within the U.S. (Pennsylvania and Iowa) where clusters of patient infections with *M. chimaera* were identified. Each of the isolates tested were associated with devices manufactured before September 2014. Samples of the water drained from the 3T devices and air samples collected while the devices were in operation were also tested. The results obtained strongly suggest that the tested 3T devices had a common source of *M. chimaera* contamination. Sequence comparisons between U.S. and European Union (EU) samples, as well as samples from the manufacturing site, would provide additional information in evaluating the potential for point source contamination at the production site. However, EU sequencing results have not been shared to date.

As new information becomes available, the FDA will evaluate the information and update its recommendations, as appropriate.

UPDATED Recommendations for Health Care Facilities and Staff:

If your facility uses 3T devices, you should:

- **Immediately remove from service any heater-cooler devices, accessories, tubing, and connectors that have tested positive for *M. chimaera* or have been associated with known *M. chimaera* patient infections at your facility.**
- **Use new accessories, tubing, and connectors to prevent recontamination when using a different heater-cooler device.**
- **Direct and channel the heater-cooler exhaust away from the patient, e.g., to the operating room exhaust vent.**
- **Be aware that device contamination also may occur from other sources such as environmental contamination or device contact with contaminated accessories.**
- **Review the recommendations in CDC's Health Advisory (<https://emergency.cdc.gov/han/han00397.asp>)**
- **Be aware that heater-cooler devices are important in patient care. In appropriately selected patients, the benefits of temperature control during open chest cardiothoracic procedures generally outweigh the risk of infection transmission associated with the use of these devices.**

If your facility has 3T devices manufactured prior to September 2014, you should:

- **Strongly consider transitioning away from the use of these devices for open-chest cardiac surgery until the manufacturer has implemented strategies for these devices to mitigate the risks of patient infection.**
 - **Use of these devices should be limited to emergent and/or life-threatening situations if no other heater cooler devices are available.**
 - **Follow the FDA's earlier recommendations to help mitigate the risks of patient infection.**
 - **Be aware that testing of heater-cooler devices to identify units contaminated with *M. chimaera* presents technical challenges related to sample collection, the long culture time, and the high rate of false negative tests. Therefore, it is not recommended at this time.**

If your facility has 3T devices manufactured after September 2014, you should:

- **Follow the FDA's earlier recommendations to help mitigate the risks of patient infection.**
- **Be aware that testing of heater-cooler devices to identify units contaminated with *M. chimaera* presents technical challenges related to sample collection, the long culture time, and the high rate of false negative tests. Therefore, it is not recommended at this time.**

The FDA recommends facilities and staff using heater-cooler units CONTINUE to implement the following measures to help reduce risk to patients:

- Strictly adhere to the cleaning and disinfection instructions provided in the manufacturer's device labeling. Ensure you have the most current version of the manufacturers' instructions for use readily available to promote adherence.
- Do not use tap water to rinse, fill, refill or top-off water tanks since this may introduce NTM organisms. Use only sterile water or water that has been passed through a filter of less than or equal to 0.22 microns. When making ice needed for patient cooling during surgical procedures use only sterile water or water that has been passed through a filter of less than or equal to 0.22 microns. Deionized water and sterile water created through reverse osmosis is not recommended because it may promote corrosion of the metal components of the system.
- Direct the heater-cooler's vent exhaust away from the surgical field to mitigate the risk of aerosolizing heater-cooler tank water into the sterile field and exposing the patient.
- Establish regular cleaning, disinfection and maintenance schedules for heater-cooler devices according to the manufacturers' instructions to minimize the risk of bacterial growth and subsequent patient infection.
- Develop and follow a comprehensive quality control program for maintenance, cleaning, and disinfection of heater-cooler devices. Your program may include written procedures for monitoring adherence to the program and documenting set up, cleaning, and disinfection processes before and after use.
- Immediately remove from service heater-cooler devices that show discoloration or cloudiness in the fluid lines/circuits, which may indicate bacterial growth. Consult your hospital infection control officials to perform the appropriate follow up measures and report events of device contamination to the manufacturer and to the FDA [via MedWatch \(/Safety/MedWatch/HowToReport/ucm2007306.htm\)](https://www.fda.gov/medwatch).
- Consider performing environmental, air, and water sampling and monitoring if heater-cooler contamination is suspected. Environmental monitoring requires specialized expertise and equipment to collect and process samples, which may not be feasible in all facilities.
- Health care facilities should follow their internal procedures for notifying and culturing patients if they suspect infection associated with heater-cooler devices.
- Submit a report to the manufacturer and to the FDA [via MedWatch \(/Safety/MedWatch/HowToReport/ucm2007306.htm\)](https://www.fda.gov/medwatch), if you suspect heater-cooler devices have been associated with patient infections.

Recommendations for Patients:

- Be aware that:
 - in the U.S., most cardiopulmonary bypass procedures involve the use of a heater-cooler device.
 - heater-cooler devices are important in patient care and, in appropriately selected patients, the benefits of temperature control necessary during open chest cardiothoracic procedures generally outweigh the risk of infection transmission associated with using these devices.
 - the FDA has received reports of patient infections associated with exposure to *M. chimaera* when contaminated 3T heater-cooler device were used during surgery.
 - *M. chimaera* infections are difficult to detect because infected patients may not develop symptoms or signs of infection for months to years after initial exposure.
 - there may be an increased risk of infection if you received a heart valve, graft, left ventricular assist device (LVAD), or any other prosthetic product/material or had a heart transplant.

- If you have undergone cardiopulmonary bypass, be aware of the possible signs and symptoms of NTM infection. These may include:
 - fatigue
 - fever
 - pain
 - redness, heat, or pus at the surgical site
 - muscle pain
 - joint pain
 - night sweats
 - weight loss
 - abdominal pain
 - nausea
 - vomiting
- If you have undergone a cardiopulmonary bypass procedure and are experiencing any of the signs and symptoms of NTM infection as outlined above, contact your health care provider as soon as possible.
- If you are not currently experiencing any changes in your general health, inform your health care provider during your next wellness visit that you have undergone a cardiopulmonary bypass procedure to determine if you require further testing or monitoring for possible exposure to NTM.

Additional information for patients is available on FDA's Heater-Cooler Devices "**Information for Patients (/MedicalDevices/ProductsandMedicalProcedures/CardiovascularDevices/Heater-CoolerDevices/ucm492585.htm)**" webpage.

FDA Activities:

On December 29, 2015, the FDA issued a **Warning Letter (/ICEC/EnforcementActions/WarningLetters/2015/ucm479684.htm)** to LivaNova PLC (formerly Sorin Group Deutschland GmbH) for its Stöckert 3T Heater-Cooler System after inspections conducted at facilities in Munchen, Germany and Arvada, Colorado revealed significant issues, including quality system and premarket clearance violations. Given the serious nature of the violations, the 3T devices manufactured by the Munchen facility are subject to import alert. This restricts the availability of the 3T devices to only those facilities that determine use of the device is medically necessary.

Sorin Group Deutschland GmbH initiated an ongoing corrective action for the 3T in July 2015, and has included updates to instructions for use with new cleaning instructions and instructions for determining if a device is contaminated with biofilm or NTM. Further updates to this recall are expected and will be evaluated by the FDA for their ability to further reduce infection risk. Please see **the FDA medical device recall database entry (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?start_search=1&knumber=K052601)** for more information regarding corrective actions by the manufacturer.

In June 2016, the FDA **convened (/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm485091.htm)** the Circulatory System Devices Panel of the Medical Devices Advisory Committee meeting and received expert clinical opinion and recommendations for patient notification and patient follow-up procedures. The panel also discussed **recommendations**

(/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM505732.pdf) for sampling and monitoring of the 3T and other heater-cooler devices, including regular visual monitoring of contamination within the water circuit, replacement of accessories (e.g. tubing) on a regular basis, and testing for water quality to assure adequate disinfection procedures are being performed. These recommendations are included in this Safety Communication.

The FDA continues to be actively engaged with the manufacturer, health care facilities and the CDC in evaluating risk and mitigation measures and will provide updates, as appropriate, as new information becomes available.

Reporting Problems to the FDA:

Device manufacturers and user facilities must comply with the applicable Medical Device Reporting (MDR) regulations (/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm2005737.htm). Health care personnel employed by facilities that are subject to the FDA's user facility reporting requirements (/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm2005737.htm) should follow the reporting procedures established by their facilities.

Prompt reporting of adverse events can help the FDA identify and better understand the risks associated with the use of medical devices. Health care providers should submit voluntary reports of infection transmission associated with heater-cooler devices or reports describing difficulty following the manufacturers' instructions for use to the agency via the Medical Device Reporting (MDR) (/MedicalDevices/Safety/ReportaProblem/ucm2005291.htm) process. If a health care provider suspects bacterial contamination of the heater-cooler device following use, we encourage the health care provider to file a voluntary report through MedWatch, the FDA Safety Information and Adverse Event Reporting program (/Safety/MedWatch/HowToReport/ucm2007306.htm).

Additional Resources:

- **FDA Communications on Heater-Cooler Devices**
 - **Mycobacterium chimaera Infections Associated with Sorin Group Deutschland GmbH Stöckert 3T Heater-Cooler System: FDA Safety Communication (/MedicalDevices/Safety/AlertsandNotices/ucm504213.htm)** (June 1, 2016) - ARCHIVED
 - **Nontuberculous Mycobacterium Infections Associated with Heater-Cooler Devices: FDA Safety Communication (/MedicalDevices/Safety/AlertsandNotices/ucm466963.htm)** (October 15, 2015)
Heater-Cooler Informational Webpage (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/CardiovascularDevices/Heater-CoolerDevices/default.htm)
- **From the Centers for Disease Control and Prevention (CDC)**
 - Perkins KM, Laws A, Hasan N, et al. **Mycobacterium chimaera Contamination of Heater-Cooler Devices Used in Cardiac Surgery — United States (https://www.cdc.gov/mmwr/volumes/65/wr/mm6540a6.htm?s_cid=mm6540a6_w)**. MMWR Morb Mortal Wkly Rep 2016;65:1117–1118. DOI **https://emergency.cdc.gov/han/han00397.asp (https://emergency.cdc.gov/han/han00397.asp)**
 - **CDC Health Advisory: CDC Advises Hospitals to Alert Patients at Risk from Contaminated Heater-Cooler Devices Used during Cardiac Surgery (https://emergency.cdc.gov/han/han00397.asp)** (October 13, 2016)
 - **Interim Guide for the Identification of Possible Cases of Nontuberculous Mycobacterium Infections Associated with Exposure to Heater-Cooler Units (http://www.cdc.gov/hai/pdfs/outbreaks/Guide-for-**

Case-Finding.pdf (May 13, 2016)

- **Non-tuberculous Mycobacterium (NTM) Infections and Heater-Cooler Devices**
(<http://www.cdc.gov/HAI/pdfs/outbreaks/CDC-Notice-Heater-Cooler-Units-final-clean.pdf>) (October 27, 2015)
- **Medical Literature:**
 - Sommerstein et al. **Transmission of *Mycobacterium chimaera* from Heater-Cooler Units during Cardiac Surgery despite an Ultraclean Air Ventilation System.** Emerg Infect Dis. 2016 June;22(6):1008-13.
 - Garvey et al.**Decontamination of heater-cooler units associated with contamination by atypical mycobacteria.** J. Hospital Infection, Volume 93, Issue 3, July 2016:229-34.

Contact Information:

If you have questions about this communication, please contact the Division of Industry and Consumer Education (DICE) at **DICE@FDA.HHS.GOV** (**<mailto:DICE@FDA.HHS.GOV>**), 800-638-2041 or 301-796-7100.

Haller S, Höller C, Jacobshagen A, Hamouda O, Abu Sin, M, Monnet, DL, Plachouras D, Eckmanns, T. Contamination during production of heater-cooler units by *Mycobacterium chimaera* potential cause for invasive cardiovascular infections: results of an outbreak investigation in Germany, April 2015 to February 2016. Euro Surveill. 2016;21(17):pii=3025. DOI: **<http://dx.doi.org/10.15585/mmwr.mm6540a6>**
(<http://dx.doi.org/10.15585/mmwr.mm6540a6>).

More in <u>Safety Communications</u> <u>(/MedicalDevices/Safety/AlertsandNotices/default.htm)</u>	
<u>Information About Heparin</u> (<u>/MedicalDevices/Safety/AlertsandNotices/ucm135345.htm</u>)	
<u>Reducing Risks Associated with Medical Device Misconnections</u> <u>(/MedicalDevices/Safety/AlertsandNotices/TubingandLuerMisconnections/default.htm)</u>	▼